August 1987:435–47

REVIEWS

Prognosis of Ventricular Arrhythmias in Relation to Sudden Cardiac Death: Therapeutic Implications

BORYS SURAWICZ, MD, FACC

Indianapolis, Indiana

The hypothesis that ventricular arrhythmias represent an independent predictor of sudden cardiac death was examined by analyzing the published data. The frequency and complexity of ventricular arrhythmias increase progressively both with age and severity of heart disease, but no age- or disease-related norms have been established for clinical guidance. Simple and complex arrhythmias, including short runs of ventricular tachycardia, do not increase risk of sudden cardiac death in subjects without heart disease or with heart disease and normal myocardial function. Progression of nonsustained into sustained ventricular tachycardia in such individuals is rare. Simple and complex ventricular arrhythmias are not strong independent predictors of sudden death in survivors of myocardial infarction. In these, the overall incidence of sudden cardiac death averages 3.5 to 5% during the first year, but is about 15 to 20% per year in patients with severely impaired ventricular function.

The results of this survey suggest that in patients with well preserved ventricular function, prophylactic use of antiarrhythmic drugs is not indicated, and that treatment of asymptomatic or mildly symptomatic ventricular arrhythmias is not likely to reduce the incidence of sudden cardiac death.

(J Am Coll Cardiol 1987;10:435–47)

The spectrum of ventricular arrhythmias ranges from a single ventricular premature complex to ventricular fibrillation. The two criteria most widely used in classifying ventricular arrhythmias in clinical practice are the frequency of ectopic complexes and the "complexity" of ventricular arrhythmias. The widespread use of ambulatory electrocardiographic (ECG) monitoring during the past two decades has generated a large amount of data about the frequency and complexity of ventricular arrhythmias in various population groups and in patients with various types of heart disease. The purpose of this report is to review this material, to evaluate the prognostic significance of ventricular arrhythmias with regard to risk of sudden cardiac death and to discuss the practical implications of the surveyed information.

From the Krannert Institute of Cardiology, Department of Medicine, Indiana University School of Medicine and the Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana. This report was based on the ISFC Lecture given at the Xth World Congress of Cardiology, Washington, D.C., September 1986. This study was supported in part by the Herman C. Krannert Fund, Indianapolis, by Grants HL-06308 and HL-07182 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, by the American Heart Association, Indiana Affiliate, Indianapolis, by the Attorney General Trust of Indiana, Indianapolis, and by the Veterans Administration, Indianapolis, Indiana.

Manuscript received October 15, 1986; revised manuscript received January 7, 1986, accepted January 14, 1987.

Address for reprints: Borys Surawicz, MD, Krannert Institute of Cardiology, 1001 West Tenth Street, Indianapolis, Indiana 46202.

Ventricular Arrhythmias in the Absence of Heart Disease

Prevalence. Ventricular arrhythmias appear to be more frequent during the neonatal period than in early childhood. In one study (1) of 202 newborns, a single ECG examination revealed eight cases of multiple ventricular premature complexes and three cases of ventricular tachycardia. All of these newborns apparently "did well." In several other studies (2), ventricular premature complexes were found in up to 25% of newborns. That such high prevalence may be due to the immaturity of the cardiac muscle, conducting system or autonomic nerves supplying the heart is suggested by the rarity of ventricular arrhythmias later in infancy and during early childhood. In children, ventricular arrhythmias are seldom found during routine ECG examination. In one study (3) of 500 children and adolescents, aged 4 to 18 years, examined at rest and during treadmill exercise, only 1 child had ventricular premature complexes. Similarly, monitoring revealed only 1 case of isolated ventricular premature complexes in 104 healthy children, aged 7 to 11 years (4). However, in another study (5) of 131 healthy boys aged 10 to 13 years, 26% had ventricular premature

0735-1097/87/$3.50

JACC Vol. 10, No. 2
August 1987:435–47

complexes, but only 2 had more than four/h and there were no complex forms of ventricular arrhythmia. The prevalence of ventricular arrhythmias appears to increase during the third decade of life. In 23 to 27 year old medical students, ambulatory monitoring revealed at least one ventricular premature complex in 50% of the subjects (6).

From their survey of the literature, Sherman et al. (7) concluded that the increase of ventricular arrhythmias in men from age 16 to 74 years was exponential. No such calculations were made for women, but no obvious sex differences are apparent from the reported monitoring results in different studies. A 24 hour ambulatory ECG showed that the prevalence was 34% in 101 healthy women aged 20 to 59 years (8), 39% in 101 asymptomatic and healthy men and women whose average age was 48.4 years (9), 46% in 147 active men aged 15 to 65 years (10), 62% in men whose average age was 55 years (11) and 69 to 100% in persons aged ≥60 years (12–16).

The prevalence of complex forms, that is, frequent or multiform ventricular premature complexes, pairs and salvos also appears to be greater in older persons. Thus, in a study (13) of 98 asymptomatic subjects aged 60 to 85 years, 36% had >30 ventricular premature complexes/h, 35% had multiform ventricular premature complexes, 11% had couplets and 4% had ventricular tachycardia. Similar prevalences were reported in 106 healthy subjects aged >75 years in England (12), and in subjects >80 years in France (14). Of 10 centenarians who underwent 24 hour ambulatory ECG monitoring (16), 9 had ventricular premature complexes and 3 had nonsustained ventricular tachycardia.

Prognostic significance. Crow et al. (17) reviewed the available evidence, including their own 12,000 cases, and concluded that a simple ventricular premature complex is not an independent risk factor for future heart disease or sudden cardiac death. In 482 insured men (18), ventricular extrasystoles were not associated with increased mortality during an average follow-up of 18 years. Similar conclusions were reached by others (10,11,19–21). In one study (10) of a group of men in whom the prevalence of ventricular premature complexes was 46%, no deaths occurred because of heart disease during a 6 year follow-up. In another study (20) of 27 individuals with frequent ventricular premature complexes, all subjects remained well at a mean interval of 8 months. A long-term (average 6.5 years) follow-up of 73 asymptomatic subjects who had frequent and complex ventricular arrhythmia including ventricular tachycardia (in 26%) showed no increased risk of death compared with that of the healthy U.S. population (21). Also, no instances of sudden death occurred in 54 subjects with ventricular premature complexes (37% complex forms) followed up for an average period of 8.3 years (22).

In infants and children, the prognosis of ventricular arrhythmias is believed to be uniformly excellent (23). At the other end of the life span, Camm et al. (12) followed up 106 healthy subjects >75 years for 18 months. Ventricular arrhythmias were present during ambulatory ECG monitoring in 69%, but there was no difference in the arrhythmia spectrum in 13 subjects who died during the follow-up, compared with the group as a whole. In the Baltimore Longitudinal Study on Aging (24), 10 (1.1%) of the healthy asymptomatic volunteers had exercise-induced ventricular tachycardia. Only one of these was <65 years old. Other findings in these subjects with ventricular tachycardia were not different from those in other healthy persons, and no one died suddenly or had syncope during a 2 year follow-up period (24).

Isolated cases of sustained ventricular tachycardia in the absence of detectable heart disease are reported in almost all of the large series of patients with this condition. In these cases, a "primary electric disease" of the heart is usually postulated, but few studies have included cardiac biopsy to rule out incipient heart disease. Sustained ventricular tachycardia can occur in children without evidence of heart disease, but the cases are rare and no deaths were reported during a long-term follow-up period (25).

Cases of sudden cardiac death due to ventricular fibrillation in the absence of demonstrable heart disease have been reported, but their rarity relegates them to the category of single case reports (26). In children, sudden death related to ventricular arrhythmias nearly always occurs in patients with an abnormal heart (27).

In conclusion, it appears that the presence of simple or complex ventricular arrhythmias, including short runs of ventricular tachycardia (sustained ventricular tachycardias appear to be extremely rare in the absence of heart disease), does not increase the risk of either cardiac death or sudden death. Evidence to the contrary has been reported in some longitudinal epidemiologic studies (28,29). However, the significance of increased mortality in subjects with ventricular premature complexes in these reports is open to question because of the low yield of arrhythmia detection in single ECGs made at rest, the limited amount of information about cardiac function, the small number of deaths and the advanced age of many victims.

Ventricular Arrhythmias in Patients With Heart Disease and Well Preserved Ventricular Function

In this category, exercise and ambulatory ECG monitoring studies have been carried out most frequently in patients with coronary artery disease without a history of myocardial infarction. Studies of patients with other heart diseases are fewer in number. It appears that the incidence and complexity of ventricular arrhythmias increase in the presence

of heart disease even when cardiac function is not appreciably impaired.

Ambulatory monitoring of patients with coronary artery disease. Of 92 patients with normal left ventricular ejection fraction studied after coronary artery bypass operations (30), 57% had complex ventricular arrhythmia and 21.5% had nonsustained ventricular tachycardia. The incidence of complications in patients with complex ventricular arrhythmias was not higher than in other patients, and there were no cardiac or sudden deaths during the follow-up period, which averaged 16 months. The investigators concluded that complex ventricular arrhythmias do not indicate poor prognosis in individuals with good left ventricular function. In 130 patients with chronic stable angina pectoris randomized to medical or surgical therapy (31), complex ventricular premature complexes during 6 hour ECG monitoring were present in 30% of surgical and 15% of medical patients but there was no difference in mortality between the two groups, and the complex arrhythmias were not associated with an increased risk of sudden cardiac death.

Thrombolysis using streptokinase intravenously was followed by ventricular arrhythmias in all patients during the first 24 hours after reperfusion (32). Although couplets occurred in 96% and nonsustained ventricular tachycardia in 89% of patients during the early period, none of these patients had serious ventricular arrhythmias at the time of discharge.

Valvular heart disease. In the study of Uretz et al. (33), frequent and complex ventricular premature complexes were present in 66% of 56 patients with valvular disease but in only 33% of 73 persons without heart disease. Review of the published data suggests that sustained ventricular tachycardia and sudden cardiac death are not common in patients with valvular disease and good ventricular function. In one series of patients with aortic valve replacement (34), only six deaths occurred in 236 patients (4%) during a mean follow-up period of 62 months.

In a study (35) of 45 patients followed up for an average of 14 months after aortic valve replacement, severity of ventricular arrhythmias appeared to correlate with the impairment of left ventricular function, and the postoperative improvement of left ventricular function was usually accompanied by reduction of frequent and complex ventricular premature complexes. In patients with mitral valve prolapse (36), frequent and complex ventricular premature complexes were more strongly associated with hemodynamically important mitral regurgitation than with mitral valve prolapse alone.

In conclusion, it appears that the presence of simple and complex ventricular arrhythmias, including short runs of ventricular tachycardia, does not increase the risk of sudden cardiac death in patients with heart disease and well preserved ventricular function.

Ventricular Arrhythmias in Survivors of Myocardial Infarction

This is a most intensively studied category of patients. In many of the earlier studies (37–42), ventricular arrhythmias recorded at various time intervals after infarction were considered to be independent predictors of increased mortality and sudden cardiac death. The validity of these conclusions is difficult to document because of the nonuniform methodology of arrhythmia detection and either absent or incomplete studies of hemodynamics, coronary anatomy, left ventricular function and wall motion abnormalities in these early studies.

Many of the recent studies (43–50) have established a strong link between the severity of ventricular arrhythmias, sudden cardiac death and impaired ventricular function. A very high incidence (61%) of sudden cardiac deaths due to arrhythmias and myocardial rupture was associated with ventricular aneurysm (43). Other serious risk factors for sudden cardiac death included the extent of myocardial infarction (44,45), low ejection fraction or poor left ventricular function (46–49) and the presence of major conduction disturbances, congestive heart failure or sustained ventricular tachycardia (50).

Sustained ventricular tachycardia is believed to be associated with more severe myocardial damage (45,51) and with large infarcts (52). Of 40 patients with sustained ventricular tachycardia within 3 to 65 days after the onset of infarction (53), only 20 were alive after an average follow-up time of 20 months, and 12 of 20 victims died suddenly. In another study (52) of 53 patients in whom sustained ventricular tachycardia or ventricular fibrillation occurred within 3 to 60 days after the onset of myocardial infarction, 24.5% died during a follow-up period averaging 15 to 18 months.

Figure 1 shows the incidence of sudden cardiac death in the survivors of myocardial infarction from published studies in which the number of patients exceeded 60, the duration of follow-up averaged at least 12 months and the incidence of sudden cardiac death was either stated or could be estimated from the reported ratio of sudden death to total death. In eight studies (46,47,54–59) the follow-up period averaged 12 to 18 months and in two (46,47) of them all sudden deaths occurred in patients with a low ejection fraction. This may account for a relatively high incidence of sudden cardiac death in these two studies. In another study (54) in which the 10.2% incidence rate of sudden cardiac death was two to three times higher than in most other studies, a low ejection fraction was an important risk factor but there was also a high incidence rate of ventricular tachycardia (11.6%), and the statistical analysis showed that arrhythmia was an independent risk factor for sudden cardiac death. In other studies (55–59), the incidence rate of sudden

JACC Vol. 10, No. 2
August 1987:435–47

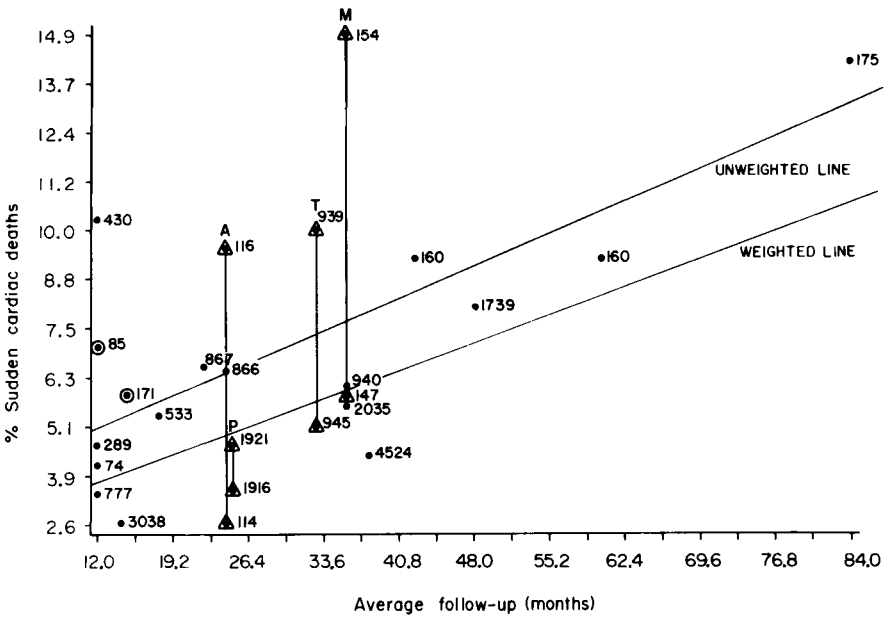

Figure 1. Incidence of sudden cardiac death at a reported average follow-up time in 21 studies (25 patient groups) from the following references: at 12 months (58,67–70); at 14 months (72); at 15 months (59); at 18 months (71); at 22 months (78); at 24 months (73,80); at 25 months (74); at 33 months (75); at 36 months (50,52,76); at 38 months (81); at 42 months (49); at 48 months (54); at 60 months (82); and at 84 months (53). The number of patients participating in each study is shown next to each **symbol.** The two **circled dots** designate two studies (46,47) in which all victims of sudden cardiac death had a low ejection fraction. The four pairs of **triangles** connected by **vertical lines** represent beta-adrenergic blocker trials (60–63) with alprenolol (A), propranolol (P), timolol (T) and metoprolol (M). In each of these trials, the group treated with beta-adrenergic blockers has a lower incidence of sudden cardiac death than does the placebo-treated group. Two **computed regression lines** have been drawn. The **lower line** shows the percent of sudden cardiac death (y) as a function of average follow-up time in months (x) weighted by sample size ($y = 2.45 + 0.956x$; $r = 0.50$; $p < 0.001$). The **upper line** shows the same relation when each study has equivalent weight ($y = 3.51 + 0.111x$; $r = 0.58$; $p = 0.003$). Note that the **weighted line** intercepts the 12 month follow-up period at 3.6%, and the **unweighted line** at 4.8%.

cardiac death ranged from 2.7 to 5.4%. A low ejection fraction or impaired ventricular function was an important risk factor for sudden cardiac death (56–58). Kleiger et al. (56) attributed increased risk of sudden cardiac death to poor ventricular function, but not to runs of ventricular tachycardia. In the Multicenter International Study (59), the incidence of sudden death after an average follow-up period of 14 months was 2.7%; some of the patients in the study were treated with practolol and some were receiving placebo, but the difference between the mortality rates in these two groups was not significant.

Studies in which the average follow-up ranged from 22 to 36 months include four trials of beta-adrenergic blockers (60–63). In each of these, the incidence of sudden cardiac death was lower in the patients receiving a beta-blocker than in those receiving placebo; that is, 2.6% for alprenolol versus 9.5% (60), 3.3% for propranolol versus 4.6% (61), 5.0% for timolol versus 10.1% (62) and 6.1% for metoprolol versus 14.9% (63). In the Beta-blocker Heart Attack Trial (BHAT) study (64) patients with congestive heart failure had more frequent and complex ventricular premature complexes and the incidence of sudden cardiac death in patients with congestive heart failure during hospitalization was 5.5% in those treated with propranolol and 10.4% in the placebo group. The corresponding incidence in patients without congestive heart failure was 2.9 and 3.3%, respectively. In two other large studies (65,66), the incidence rate of sudden cardiac death was 6.2 and 6.6%, respectively. In one of these (65), ischemia preceded the terminal event in 66% of patients with witnessed arrhythmic death.

In three studies (38,40,67) in which the follow-up period averaged 36 to 38 months, the incidence rate of sudden cardiac death was 4.3 (67), 5.5 (38) and 5.9% (40), respectively; hemodynamic assessment of patients in these studies was not performed. In four studies (37,41,42,68) in which the follow-up period averaged 42 to 84 months, the incidence rate of sudden cardiac death was 9.4 (37), 8 (42), 9.4 (68) and 14.3% (41), respectively; no hemodynamic

Table 1. Two Year Mortality in Relation to Frequency of Ventricular Premature Complexes/h and to Left Ventricular Ejection Fraction at the Time of Hospital Discharge After Myocardial Infarction in 766 Patients

	VPCs/h (%)						
LVEF	0	<1	1 to 2.9	3 to 9.9	10 to 29.9	≥30	Total*
≤39% (n = 256)	20	11.6	16	25	20	29	19.1
<40% (n = 510)	3.4	6	8	17	12.5	8	9.8

*Of all deaths, 60.7% were attributed to arrhythmia, that is, 11.5% in the lower ejection fraction group and 6% in the higher ejection fraction group. See text for discussion. LVEF = left ventricular ejection fraction; VPC = ventricular premature complex. (The data are rearranged, with permission, from Table 3 in Bigger JT Jr, et al. [69].)

assessment was performed in these studies. In one of these (68), the incidence of sudden cardiac death shown in Figure 1 may not be entirely accurate because the follow-up was incomplete.

Of particular interest are three recent studies included in Figure 1 (57,58,69) because of careful evaluation of ventricular function in large groups of patients. In two of these (58,59), ventricular arrhythmia was an independent risk factor for sudden cardiac death. In the Multicenter study (69), 866 survivors of myocardial infarction were followed up for 2 years; there were 89 deaths, of which 54 were attributed to arrhythmias. The left ventricular ejection fraction in this group is not listed separately, but the study concludes that "ventricular arrhythmias and left ventricular dysfunction are independently related to mortality risk." From Table 3 in that paper (69), I rearranged the data to separate the patients into two categories, that is, 256 with an ejection fraction <39% and 510 with an ejection fraction >40% (Table 1). This table shows the relation between 2 year mortality and the frequency of ventricular premature complexes in these two groups. In each category, the mortality is higher in subjects with a low ejection fraction, and in neither group does the mortality increase progressively with increasing ventricular premature complex frequency.

In the MILIS study (58), 533 survivors of myocardial infarction were followed up for an average of 18 months, and the conclusion was that "the presence of frequent [ventricular premature depolarizations] in association with left ventricular dysfunction identifies patients at high risk for sudden death over the next 7 months." This conclusion is based on their data, reproduced in Table 2, which show that the incidence of sudden cardiac death in patients with a left ventricular ejection fraction >40%, that is, Groups A and C, was 8 (2.3%) of 352, and in those with an ejection fraction <40%, that is, Groups B and D, 21 (11.6%) of 181. This is a highly significant difference ($p < 0.001$). Also the difference between the incidence of sudden death in Group A versus Group B is highly significant ($p < 0.001$). This confirms the independent significance of left ventricular ejection fraction. The independent statistical significance of ventricular premature depolarizations >10/h emerges from the comparison of Groups A and C. However, this is a weak significance ($p = 0.045$) that ceases to exist ($p = 0.168$) if only one of three cases of sudden cardiac death in Group

Table 2. Incidence of Sudden Cardiac Death During a 2 Year Follow-up in 533 Patients Classified Into Four Groups on the Basis of Left Ventricular Ejection Fraction >40% and <40%, and Ventricular Premature Depolarizations >10 and <10/h

	Sudden Cardiac Deaths	p Value
Group A LVEF ≥40%, VPD <10/h	5 of 314 (2%)	
Group B LVEF <40%, VPD <10/h	14 of 141 (10%)	
Group C LVEF ≥40%, VPD ≥10/h	3 of 38 (8%)	
Group D LVEF <40%, VPD ≥10/h	7 of 40 (18%)	
LVEF ≥ 40% (A + C) vs. LVEF <40%	(B + D) = 8 of 352 vs. 21 of 181	<0.001
In patients with VPD ≥10/h:	C vs. D = 3 of 38 vs. 7 of 40	0.312
In patients with VPD <10/h: VPD >10/h vs. VPD <10/h	A vs. B = 5 of 314 vs. 14 of 141	<0.001
In patients with LVEF ≥40°:	A vs. C = 5 of 314 vs. 3 of 38	0.045
In patients with LVEF <40°:	B vs. D = 14 of 141 vs. 7 of 40	0.260

Fisher's exact test was used to evaluate the differences between groups. Discussion in text. LVEF = left ventricular ejection fraction; VPD = ventricular premature depolarizations. (Reproduced with permission from Mukharji J, et al. [58].)

JACC Vol. 10, No. 2
August 1987:435–47

C is removed.* Maisel et al. (57) followed up 191 survivors of non-Q wave myocardial infarction and 586 survivors of Q wave infarction. The presence of complex ventricular premature complexes at the time of hospital discharge was an important predictor of mortality in patients with a non-Q wave infarction but not in those with a Q wave infarction. In the non-Q wave infarction group, the mortality rate was 19.4%. It was 8.8%, that is, 10 of 113, in those with noncomplex ventricular premature complexes and 34.6%, that is, 27 of 78, in those with complex ventricular premature complexes. Because approximately 50% of deaths were classified as sudden, the 10% incidence rate of sudden cardiac deaths within 1 year in this group is much higher than in most other studies. The authors suggest that this may be due to an "unstable ischemic state" in these patients.

In two studies (70,71) not included in Figure 1, no relation was found between sudden cardiac death and complex ventricular arrhythmias in survivors of myocardial infarction, followed up for up to 12 years in one (70) and for 2 years in the other (71). In the latter study, sudden death occurred in 4 of 31 survivors, but none of these had frequent or complex ventricular premature complexes on the predischarge ambulatory ECG, whereas none of the 5 patients who had such arrhythmias before discharge died suddenly.

Ventricular Arrhythmias in Other Patients With Coronary Artery Disease

It has been firmly established (72–74) that the prognosis of patients with coronary artery disease depends on the severity and extent of the disease, and that at each level of severity, mortality is augmented by the presence of scars and aneurysm. In the study of Blevins et al. (75), the mortality rate averaged 10% in patients with an ejection fraction >40%, and 60% in those with an ejection fraction <40%.

The role of ventricular arrhythmias as an independent risk factor remains uncertain. In the study of Califf et al. (76), 23% of 1,293 patients (of whom 620 had significant coronary artery disease) had ventricular arrhythmias during treadmill exercise after coronary arteriography. Of these, 18% had simple ventricular premature complexes, 3% had couplets and 2% had ventricular tachycardia. Arrhythmia was a marker of left ventricular dysfunction and did not contribute independently to the prediction of survival or sudden cardiac death once the catheterization data were known. These conclusions were challenged (69) because: 1) it was a stress test and not ambulatory monitoring of the ECG; 2) patients admitted for evaluation of arrhythmia were excluded; and 3) only 53% of patients had a history of myocardial infarction, and in many the infarction was remote. However, similar results were obtained in a study by Lichtlen et al. (77), who followed up 204 patients for an average of 18.2 months; sudden cardiac death occurred in 9.3%. Both the sudden cardiac deaths and ventricular arrhythmias occurred in patients with more severe left ventricular dysfunction, and the severity of arrhythmias was not an independent prognostic factor. In another study (78), patients with an ejection fraction <30% had more ventricular arrhythmias than did those with an ejection fraction >30%, and the prognostic factor of importance appeared to be the presence of myocardial ischemia.

Ventricular Arrhythmias in Patients With Severely Impaired Ventricular Function

Studies in these patients can be separated into two categories depending on whether the main focus of investigation was primarily the treatment of congestive heart failure or the treatment of symptomatic ventricular arrhythmias.

Class III to IV patients with congestive heart failure due to ischemic or idiopathic dilated cardiomyopathy. Packer (79) summarized the results of seven studies comprising 891 patients in whom the total mortality rate averaged 37.4%, and the rate of sudden cardiac death 14.3%/year. The incidence of ventricular tachycardia in different studies ranged from 39 to 60%. Similar findings were present in an additional eight studies (80–87) not reviewed by Packer comprising a total of 398 patients. In these, the total mortality rate averaged 42.4%, and the average incidence rate of sudden cardiac death was 21.4% during a follow-up period averaging 18.5 months and ranging from 11 to 34 months. The incidence rate of nonsustained ventricular tachycardia in these studies ranged from 49 to 100%, and averaged 65%.

In 9 of 13 of these studies in which the relation was considered, sudden cardiac death was unrelated to nonsustained ventricular tachycardia. Although the role of antiarrhythmic drugs received by many patients treated for congestive heart failure has not been assessed, it remained uncertain whether the treatment of arrhythmias in this category of patients affected their survival (87,88). Also, the incidence of nonarrhythmic death in patients with arrhythmias is very high. In one study (86), ventricular tachycardia was present in 26 of 35 patients. Of these, 80% died within 2 years, and only one of these deaths was attributed to arrhythmia.

Even in those few studies (82–84) in which ventricular

* Conversely, if the number of sudden cardiac deaths in Group C is increased from three to four, the probability (p) value becomes 0.01. Similarly, if the number of deaths in Group A is decreased from five to four, the p value is 0.03, whereas if it is increased to six, the p value is 0.06. Thus, a change of only one death in either group can change the p value to either nonsignificant or to more significant. This instability is indicative of the weakness of the association. By contrast, a change of the number of deaths in either direction in the groups with contrasting left ventricular ejection fractions does not change the significance of Fisher's exact test.

arrhythmia had an independent prognostic significance, the correlation was not strong. For instance, in the study of Holmes et al. (83), of 31 patients with ischemic and dilated idiopathic cardiomyopathy, 9 had simple and 22 had complex ventricular premature complexes. During the follow-up averaging 25 months, 1 death occurred in the former and 13 deaths (11 sudden) in the latter group. However, although complex ventricular premature complexes were an independent risk factor for sudden cardiac death, a pulmonary capillary wedge pressure >16 mm Hg was present in 2 of 8 patients with simple, but in 19 of 22 patients with complex ventricular premature complexes. In another study (82), 19 deaths (12 sudden) occurred after an average follow-up period of 11 months in 74 patients with idiopathic dilated cardiomyopathy. All patients who died had an ejection fraction <40%. The left ventricular diastolic pressure and cardiac index averaged 11 mm Hg and 3.1 liters/min per m^2, respectively, in the survivors, and 22 mm Hg and 2.5 liters/min per m^2, respectively, in the victims of sudden cardiac death. Ventricular tachycardia was present in 9 of the 12 patients who died suddenly and in 27 of the 62 survivors. In yet another study (84) of 69 patients with dilated cardiomyopathy, mortality at 1 year was 35%. Of 48 patients with frequent, complex ventricular premature complexes and nonsustained ventricular tachycardia, 14 died, and of 25 patients with no or rare premature ventricular complexes, 4 died. Multivariate analysis revealed that ventricular arrhythmia contributed independently to mortality but could not distinguish between death due to heart failure and death due to arrhythmia.

Patients with symptomatic ventricular tachyarrhythmias. Of six representative studies (75,89–93) in this category, five include patients with sustained ventricular tachycardia or those resuscitated from cardiac arrest (89–93) and one (75) includes patients with frequent and complex ventricular arrhythmias. In five of the six studies, 81 to 100% of patients had either coronary artery disease or cardiomyopathy, and in one study (89) only 72% had these diagnoses. Two groups were treated with amiodarone (92,93) and the remaining with diverse drugs, including amiodarone. The total number of patients in these studies was 549, the average follow-up was 14.8 months (8.5 to 24 months) and the incidence of sudden cardiac death ranged from 8.2% (89) in 1 year to 45.4% in 2 years (75). Severity of heart disease was considered to be the strongest independent predictor of mortality in the two largest studies encompassing 239 in one (91) and 123 patients in the other (89).

Prognosis of Patients Resuscitated From Cardiac Arrest

The survivors of cardiac arrest appear to be at high risk of recurrences. In several studies (94–97), sudden death occurred in 26% of 61 patients during a follow-up period averaging 23.6 months (94), in 26.4% of 227 patients during a follow-up period averaging 35 months (95), in 16% of 62 patients during a follow-up period averaging 22 months (96) and in 12% of 139 patients during the first year (97). It has been reported (68,98) that the prognosis of patients resuscitated from ventricular fibrillation at the onset of myocardial infarction is not worse than that of other survivors of myocardial infarction. If, however, myocardial infarction does not evolve after an episode of acute ischemia associated with ventricular fibrillation, the resuscitated patients are at higher risk of recurrences, presumably because the factors that precipitated the initial episode have not ceased to exist. In two studies (99,100), sudden death occurred in 34% of 116 (99) and in 34% of 80 (100) survivors of cardiac arrest, not followed by myocardial infarction, during follow-up periods averaging 14 to 16 months. In one of these (100), the prognosis correlated with the severity of left ventricular dysfunction and of coronary artery disease.

R on T Phenomenon

Is it futile to control ventricular arrhythmias when the ultimate outcome is determined by the condition of the heart? This question was posed by Calvert et al. (101) while discussing their own findings, which showed that the incidence and complexity of ventricular arrhythmias in 124 patients monitored before coronary arteriography paralleled the severity of coronary artery disease, myocardial asynergy and level of left ventricular end-diastolic pressure. The answer to this rhetorical question was "no," because it was postulated that the mere presence of ventricular arrhythmias can create risk of a fatal "accidental discharge" during the vulnerable period. This period is believed to correspond to the terminal portion of the T wave, and a premature complex interrupting the T wave has been referred to as the R on T phenomenon. There is little doubt that the R on T phenomenon frequently initiates ventricular fibrillation in the prehospital and early hospital phase of acute myocardial infarction. Also, it frequently initiates a ventricular tachyarrhythmia, in particular torsade de pointes, in the setting of hypokalemia or long QT interval of various origins (102). However, under all other circumstances, the R on T phenomenon is no more dangerous than is any other ventricular premature complex (102).

This conclusion emerged from a review of studies (102) that monitored patients with ventricular tachycardias during the acute and late hospital phases of myocardial infarction, survivors of myocardial infarction, miscellaneous patient groups with ventricular arrhythmias, exercise-induced ventricular tachycardias and subjects without heart disease. In a number of these studies, ventricular tachycardia tended to occur after a late rather than after an early ventricular premature complex. Therefore, in practice, the evaluation of coupling intervals and prematurity indexes of the ventricular

JACC Vol. 10, No. 2
August 1987:435–47

ectopic complexes has not influenced the clinical approach to ventricular arrhythmias.

Sudden Cardiac Death

Sudden cardiac death may be unexpected in both its victim and its timing when it afflicts individuals not known either to have heart disease or to be at risk of sudden death. Alternatively, the death may be unexpected in time only when the person is known to be at risk. In both categories, in the adult population in this country, the vast majority of victims have coronary artery disease. Since the advent of coronary arteriography, it has been known that mortality increases with the extent and severity of coronary artery disease, and the presence of scars and aneurysms. Table 3 shows the mortality in the Cleveland Clinic study (72). The incidence of sudden cardiac death is given only for persons with absent or mild coronary artery disease. The calculations from this small number of patients studied for 5 years show that the incidence of sudden cardiac death/year per 1,000 population is about 10 times greater in subjects with ≤50% coronary narrowing than in those without angiographic evidence of coronary artery disease.

It has been estimated that 300,000 sudden cardiac deaths occur each year in the United States (103). The incidence of sudden cardiac death in person and time can be estimated from long-term epidemiologic studies. In the Tecumseh study (28), 5,129 individuals past age 16 were followed up for 6 years, and 45 sudden deaths occurred during a 6 year follow-up period; this gives an incidence of 1.46 sudden deaths/year per 1,000 population. In the Framingham study (103), 112 sudden cardiac deaths occurred during a 26 year follow-up of 5,127 persons who were free of manifest coronary heart disease at the time of examination, that is, there was an incidence of 0.84 sudden cardiac death/year per 1,000 population. In the Manitoba study (104) of 3,983 male members of the Canadian Air Force with a mean age of 30.8 years at entry who were followed up for 30 years, the calculated incidence was 0.58 sudden cardiac death/year per 1,000 population. In the male factory workers in Canton, North Carolina who entered the study at the age of 35 to 69 years (105), the incidence of sudden cardiac death was 2.0/year per 1,000 population. The Tecumseh and the Framingham studies (28,103) appear suitable for a general estimate because they contain approximately equal numbers of men and women. An average incidence of sudden cardiac death/year per 1,000 population in these studies is 1.15. Because the number of men >30 and women >40 years equals about 107 million in the United States, the estimated number of sudden cardiac deaths unexpected both in person and in time is about 123,000. The remaining 177,000 will occur in subjects with known heart disease. From Figure 1, the incidence of sudden cardiac death does not appear to exceed 4 to 5% during the first year. The estimated number of sudden cardiac death victims at the end of the first year is 36,000 to 45,000. This suggests that the remaining 132,000 to 141,000 victims are predominantly individuals with more remote myocardial infarction and also those with cardiomyopathy and other miscellaneous types of heart disease.

Common to all studies of sudden cardiac death was the finding of higher incidence among male subjects, particularly in the younger age groups, and the increasing incidence with age in both sexes. In the Framingham study (106), the risk of sudden death was increased threefold in the general population with compared with those without ventricular premature complexes. However, virtually all patients with ventricular premature complexes who died suddenly had other ECG abnormalities. Also, in persons with known coronary artery disease, the proportion of those who died suddenly was the same among those with and without ventricular arrhythmias. This finding complements the evidence obtained from the monitoring studies discussed earlier that ventricular arrhythmias are not causally related to sudden death.

Table 3. Results of a 5 Year Follow-up in the Cleveland Clinic Study of Patients Undergoing Coronary Angiography and Not Treated Surgically

Coronary Arteries	No. of Patients	Total Cardiac Deaths [No. (%)]	Sudden Cardiac Deaths [No. (%)]	SCD Incidence per 1,000/year
Normal	342	2 (0.6)	2 (0.6)	1.17
<30% Narrowing	101	6 (5.9)	2 (2.0)	3.96
30 to 50% Narrowing	57	3 (5.3)	3 (5.3)	10.5
<50% One vessel	202	29 (14.4)		
>50% Two vessels	233	88 (37.8)		
>50% Three vessels	118	63 (53.4)		
>50% Left main coronary artery	37	21 (56.8)		

See text for discussion. SCD = sudden cardiac death. (Reproduced with permission from Bruschke AVG et al. [72].)

Uniqueness of Electrical Accidents Causing Sudden Death

The lack of relation between ventricular arrhythmias and sudden cardiac death makes the ventricular premature complex hypothesis of sudden cardiac death (107) untenable, and suggests that electrical disorganization is a result of a unique accident related to the presence of a unique electrophysiologic abnormality, or a unique constellation of such abnormalities. Two such abnormalities have been suggested in the discussion of the R on T phenomenon, association with a long QT interval and presence of acute myocardial ischemia. Of these, myocardial ischemia is, by far, numerically more prevalent.

The strongest evidence implicating myocardial ischemia as the cause of fatal electrical accidents is the timing of ventricular fibrillation in patients with acute myocardial infarction. In these, ventricular fibrillation occurs frequently during the prehospital or early hospital phase (108–110) but seldom occurs thereafter. In one study (111) of 98 patients who constituted 20% of all cases of acute myocardial infarction, ventricular fibrillation occurred in all but 1 within 10 hours after the onset of symptoms.

Ischemia is implicated when ventricular fibrillation is preceded by ST segment depression during or after exercise or by ST segment elevation induced by coronary spasm (112,113). Serious ventricular arrhythmias have been recorded during variant angina pectoris episodes in about 50% of patients (114,115). These arrhythmias have occurred during maximal ST segment elevation (occlusion arrhythmias) (114–116) or during resolution (reperfusion arrhythmias) (117). In a study (118) of 114 patients with variant angina followed up for an average of 26 months, 6 died suddenly and 13 were resuscitated from cardiac arrest; ST segment elevation was greater in the sudden death-cardiac arrest group. The link between arrhythmias and ischemia was also suggested by observations that maximal ST segment elevation was significantly greater in patients who had occlusion arrhythmias than in those who had no arrhythmias (114,115), that complex ventricular arrhythmias tended to occur when the ST segment elevation was increasing or reaching maximum (119) and that the severity of ventricular arrhythmias was related to the magnitude of ST segment elevation and other markers of ischemia (120).

To be valid, the ischemia hypothesis of sudden cardiac death requires proof that effective treatment and prevention of myocardial ischemia reduces the incidence of sudden cardiac death. The evidence suggestive of this is the reduced incidence of sudden cardiac death in survivors of myocardial infarction treated with beta-adrenergic blockers and in certain patients after coronary artery bypass graft operations. It is of interest that in the BHAT study (121), propranolol was equally beneficial in patients with and without ventricular arrhythmias. The benefit of preventive therapy may be difficult to demonstrate in individual patients, but cases of ventricular tachycardia or ventricular fibrillation ceasing to recur after coronary artery bypass operation (122) or after percutaneous angioplasty (123) have been reported.

Lethal arrhythmias associated with a long QT interval or an abnormal repolarization may be related to increased dispersion of ventricular repolarization or triggered afterdepolarizations, or both (102). Barring the unrecognized or latent cases of congenital long QT syndrome, most electrical accidents of this type can be reduced substantially by the prevention of contributing factors such as hypokalemia, hypomagnesemia (?), fad diets and adverse effects of certain antiarrhythmic and certain psychotropic drugs.

Therapeutic Implications

Although ambulatory ECG monitoring has documented that the prevalence and complexity of ventricular arrhythmias increase with age and severity of heart disease, there are no established averages or ranges of frequency and complexity expected for various ages, types and stages of heart disease. The absence of norms makes it impossible to determine whether any given finding deviates from the values expected for the given individual. This, in turn, makes it difficult to define therapeutic objectives in the absence of symptoms.

There are no studies showing that treatment of arrhythmias with drugs, other than the beta-adrenergic blockers, reduces the incidence of sudden and nonsudden cardiac death. Accordingly, the absence of independent prognostic significance of ventricular arrhythmias implies that their treatment should be confined to patients with serious symptoms. Prophylactic use of antiarrhythmic drugs in asymptomatic or mildly symptomatic patients is justifiable only in patient groups for which evidence exists that ventricular arrhythmias are moderately strong predictors of sudden cardiac death. At this time, this has apparently been documented only for patients with obstructive cardiomyopathy and nonsustained ventricular tachycardia (124), and the survivors of non-Q wave myocardial infarction (57). However, even in the latter patient group, the arrhythmia may be a marker of myocardial ischemia.

Clinical Trials in Survivors of Myocardial Infarction

The survivors of myocardial infarction form a cohort of unique epidemiologic importance for two reasons: 1) they represent numerically the largest population group at risk of sudden cardiac death, and 2) they can be easily stratified with respect to the risk factors and to the results of more or less uniform diagnostic studies of cardiac function. These patients, conveniently located in the hospital, become the

JACC Vol. 10, No. 2
August 1987:435–47

most appropriate candidates for clinical trials designed to test the role of various interventions on morbidity and mortality, including sudden cardiac death. Of seven trials of antiarrhythmic agents conducted so far, and summarized by Furberg and May (125), in one, both the drug and the placebo produced the same results; in two, the drug improved the outcome, and in four, the drug worsened it. However, in none of these studies did the results achieve significance, possibly because of the small numbers of enrolled patients (range 150 to 630) and the exclusion of patients with severe ventricular arrhythmias.

It may be postulated that to achieve conclusive results in trials of this type: 1) ventricular arrhythmias must constitute a strong, independent risk factor; 2) the incidence of sudden cardiac death in a group of subjects with fairly uniform characteristics must be substantial; and 3) the drug used in the trial must be effective, nontoxic, affordable and convenient to use. The foregoing literature survey fails to provide an unequivocal answer to the question of whether ventricular arrhythmias represent an independent risk factor for sudden cardiac death in the survivors of myocardial infarction. This cannot be attributed to either a paucity of studies or an inadequate design of the conducted trials. Most likely, the lack of conclusive results reflects either an absent or, at best, a weak correlation between ventricular arrhythmias and sudden death within a large pool of survivors of myocardial infarction. Therefore, it would appear logical to limit trials to those groups of patients in whom ventricular arrhythmias represent a strong independent risk factor for arrhythmic cardiac death.

Another drawback of studying a large pool of survivors of myocardial infarction is inherent in wide variations of the incidence of sudden cardiac death in different population groups, some explained by known factors such as age and ventricular function, others remaining unexplained (66). Assuming the widely quoted occurrence of 1 million cases of infarction in a year in the United States, a 10% hospital mortality rate and an average 8% mortality rate during the first year after infarction, there are 900,000 immediate and 828,000 1 year survivors of myocardial infarction. As calculated earlier, the estimated number of sudden cardiac death victims at the end of the first year is 36,000 to 45,000. Assuming that a drug causes a 25% reduction of the incidence of sudden cardiac death, 9,000 to 11,250 lives would be saved during the first year by treating 900,000 survivors of myocardial infarction during this period.

No trial can neglect serious difficulties in assessing the results of any drug therapy resulting from spontaneous variability of untreated arrhythmias. Thus, in the study of Pratt et al. (126) during two periods of placebo treatment in symptomatic but not life-threatening ventricular arrhythmias, the number of ventricular premature complexes decreased by 50%, of pairs by 65% and of ventricular tachycardia by 85% during the second period of placebo administration.

Another difficulty in evaluating the results of drug therapy is the inability to distinguish between better drug tolerance and greater drug efficacy. In the study of 155 patients by Velebit et al. (127), in 53 (34.2%) at least one drug worsened the arrhythmia and in 80 (11.1%) of 722 trials the drug worsened or provoked arrhythmia. Also, the response to antiarrhythmic therapy appears to depend on ventricular function, being more effective in patients with a higher left ventricular ejection fraction (128) and more difficult to suppress when the ejection fraction is low (75).

We gratefully acknowledge the help of Naomi S. Fineberg, PhD for statistical evaluation of the data.

References

1. Southall DP, Orell MJ, Talbot JF, et al. Study of cardiac arrhythmias and other forms of conduction abnormality in newborn infants. Br Med J 1977;2:597–9.
2. Boning U, Brodherr-Heberlein S, Schreiber R, Schumacher G, Buhlmeyer K. Extrasystole in the neonatal period. Geburtshilfe Frauenheilkd 1985;45:803–8.
3. Greco R, Musto B, Siciliano S, et al. Prevalence of hyperkinetic arrhythmias in a healthy infantile and adolescent population: correlations between standard ECG, stress test and dynamic ECG. G Ital Cardiol 1983;13:179–83.
4. Southall DP, Richards J, Mitchell P, Brown DJ, Johnston PGB, Shinebourne EA. Study of cardiac rhythm in healthy newborn infants. Br Heart J 1980;43:14–20.
5. Scott O, Williams GJ, Fiddler GI. Results of 24-hour ambulatory monitoring of electrocardiogram in 131 healthy boys aged 10 to 13 years. Br Heart J 1980;44:304–8.
6. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24-hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. Am J Cardiol 1977;39:390–4.
7. Sherman H, Sandberg S, Fineberg HV. Exponential increase in age-specific prevalence of ventricular dysrhythmias among males. J Chronic Dis 1982;35:743–50.
8. Romhilt DW, Chaffin C, Choi SC, Irby EC. Arrhythmias on ambulatory electrocardiographic monitoring in women without apparent heart disease. Am J Cardiol 1984;54:582–6.
9. Kostis JB, McCrone K, Moreyra AE, et al. Premature ventricular complexes in the absence of identifiable heart disease. Circulation 1981;63:1351–6.
10. Orth-Gomer K, Hogstedt C, Bodin L, Soderholm B. Frequency of extrasystoles in healthy male employees. Br Heart J 1986;55:259–64.
11. Hinkle LE, Carver ST, Stevens M. The frequency of asymptomatic disturbances of cardiac rhythm and conduction in middle-aged men. Am J Cardiol 1969;24:629–50.
12. Camm AJ, Evans KE, Ward DE, Martin A. The rhythms of the heart in active elderly subjects. Am Heart J 1980;99:598–604.
13. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population. Chest 1982;81:302–7.
14. Kantelip JP, Sage E, Duchene-Marallaz P. Findings on ambulatory electrocardiographic monitoring in subjects older than 80 years. Am J Cardiol 1986;57:398–401.

15. Glasser SP, Clark PI, Applebaum HJ. Occurrence of frequent complex arrhythmias detected by ambulatory monitoring. Chest 1979;75:565–8.

16. Callaham P, Kinzel T, Kuo CS, Wekstein D, DeMaria A. Electrophysiologic characteristics of centenarians: evaluation by resting and ambulatory ECG (abstr). J Am Coll Cardiol 1986;7:52A.

17. Crow R, Prineas R, Blackburn H. The prognostic significance of ventricular ectopic beats among the apparently healthy. Am Heart J 1981;101:244–8.

18. Rodstein M, Wolloch L, Gubner RS. Mortality study of the significance of extrasystoles in an insured population. Circulation 1971;44: 617–25.

19. Desai DC, Hersberg PI, Alexander S. Clinical significance of ventricular premature beats in an outpatient population. Chest 1973;64: 564–9.

20. Montague TJ, McPherson DD, MacKenzie BR, et al. Frequent ventricular ectopic activity without underlying cardiac disease: analysis of 45 subjects. Am J Cardiol 1983;52:980–4.

21. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. N Engl J Med 1985;312:193–7.

22. Elkon KB, Swerdlow TA, Myburgh DP. Persistent ventricular ectopic beats: a long-term study. S Afr Med J 1977;52:564–6.

23. Krongrad E, Hordof AJ. Tachycardias in children. In: Surawicz B, Reddy CP, Prystowsky EN, eds. Tachycardias. Boston: Martinus Nijhoff, 1984:319–54.

24. Fleg JL, Lakatta EG. Prevalence and prognosis of exercise-induced nonsustained ventricular tachycardia in apparently healthy volunteers. Am J Cardiol 1984;54:762–4.

25. Fulton DR, Chung KJ, Tabakin BS, Keane JF. Ventricular tachycardia in children without heart disease. Am J Cardiol 1985;55:1328–31.

26. Lown B, Temte JV, Reich P, Gaughan C, Regestein Q, Hai H. Basis for recurring ventricular fibrillation in the absence of coronary heart disease and its management. N Engl J Med 1976;294:623–9.

27. Garson A Jr, Smith RT, Moak JP, Ross BA, McNamara DG. Ventricular arrhythmias and sudden death in children. J Am Coll Cardiol 1985;5:130B–3B.

28. Chiang BN, Perlman LV, Ostrander LD, Epstein RH. Relationship of premature systoles to coronary heart disease and sudden death in the Tecumseh epidemiology study. Ann Intern Med 1969;70:1159–66.

29. Cullen K, Wearne KL, Stenhouse NS, Cumpston GN. Q waves and ventricular extrasystoles in resting electrocardiograms. A 16-year follow-up in Busselton study. Br Heart J 1983;50:465–8.

30. Rubin DA, Nieminski KE, Monteferrante JC, Mages T, Reed GE, Herman MV. Ventricular arrhythmias after coronary artery bypass graft surgery: incidence, risk factors and long-term prognosis. J Am Coll Cardiol 1985;6:307–10.

31. De Soyza N, Murphy ML, Bissett JK, Kane JJ, Doherty JE. Ventricular arrhythmia in chronic stable angina pectoris with surgical or medical treatment. Ann Intern Med 1978;89:10–4.

32. Cercek B, Lew AS, Laramee P, Shah PK, Ganz W, Peter T. The high prevalence of ventricular arrhythmias in the 24 hours following reperfusion does not indicate a high risk for subsequent severe arrhythmias (abstr). J Am Coll Cardiol 1986;7:240A.

33. Uretz EF, Denes P, Ruggie N, Vasilomanolakis E, Messer JV. Relation of ventricular premature beats to underlying heart disease. Am J Cardiol 1984;53:774–80.

34. Lytle BW, Ellis J, Maloney JD, Cosgrove DM, Goormastic M, Loop FD. Late survival after isolated aortic valve replacement for 236 patients; influence of ventricular arrhythmias (abstr). J Am Coll Cardiol 1986;7:161A.

35. Olshausen K, Amann E, Hoffman M, Schwarz F, Mehmel HC, Kubler W. Ventricular arrhythmias before and late after aortic valve replacement. Am J Cardiol 1984;53:142–6.

36. Kligfield P, Hochreiter C, Kramer H, et al. Complex arrhythmias in mitral regurgitation with and without mitral valve prolapse: contrast to arrhythmias in mitral valve prolapse without mitral regurgitation. Am J Cardiol 1985;55:1545–9.

37. Kotler MN, Tabatznik B, Mower MM, Tominaga S. Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post-infarction period. Circulation 1973;47:959–66.

38. The Coronary Drug Project Research Group. Prognostic importance of premature beats following myocardial infarction. Experience in the Coronary Drug Project. JAMA 1973;223:1116–24.

39. Vismara LA, Vera Z, Foerster JM, Amsterdam EA, Mason DT. Identification of sudden death risk factors in acute and chronic coronary artery disease. Am J Cardiol 1977;39:821–8.

40. Moss AJ, Davis HT, De Camilla J, Bayer LW. Ventricular ectopic beats and their relation to sudden and non-sudden cardiac death after myocardial infarction. Circulation 1979;60:998–1003.

41. Van Gelder AL, Goldman AP, Myburgh DP. Prognostic significance of ventricular ectopic beats in chronic ischaemic heart disease. S Afr Med J 1979;56:167–9.

42. Ruberman W, Weinblatt E, Goldberg JD, Frank CW, Chaidhary BS, Shapiro S. Ventricular premature complexes and sudden death after myocardial infarction. Circulation 1981;64:297–305.

43. Meizlish JL, Berger HJ, Plankey M, Errico D, Levy W, Zaret BL. Functional left ventricular aneurysm formation after acute anterior transmural myocardial infarction. N Engl J Med 1984;311:1001–6.

44. Geltman EM, Ehsani AA, Campbell MK, Schechtman K, Roberts R, Sobel BE. The influence of location and extent of myocardial infarction on long-term ventricular dysrhythmia and mortality. Circulation 1979;60: 805–14.

45. Braat SH, de Zwaan C, Brugada P, et al. Value of left ventricular ejection fraction in extensive anterior infarction to predict development of ventricular tachycardia. Am J Cardiol 1983;52:686–9.

46. Kelly MJ, Thompson PL, Quinlan MF. Prognostic significance of left ventricular ejection fraction after acute myocardial infarction: a bedside radionuclide study. Br Heart J 1985;53:16–24.

47. Olson HG, Lyons KP, Troop P, Butman SM, Piter KM. Prognostic implications of complicated ventricular arrhythmias early after hospital discharge in acute myocardial infarction: a serial ambulatory electrocardiography study. Am Heart J 1984;108:1221–8.

48. Marchlinski FE, Waxman HL, Buxton AE, Josephson ME. Sustained ventricular tachyarrhythmias during the early post-infarction period: electrophysiologic findings and prognosis for survival. J Am Coll Cardiol 1983;2:240–50.

49. Borer JS, Rosing DR, Miller RH, et al. Natural history of left ventricular function during 1 year after acute myocardial infarction; comparison with clinical, electrocardiographic and biochemical determinations. Am J Cardiol 1980;46:1–12.

50. Waspe LE, Seinfeld D, Ferrick A, Kim SG, Matos JA, Fisher JD. Prediction of sudden death and spontaneous ventricular tachycardia in survivors of complicated myocardial infarction: value of response to programmed stimulation using a maximum of three ventricular extrastimuli. J Am Coll Cardiol 1985;5:1292–1301.

51. Anderson KP, De Camilla J, Moss AJ. Clinical significance of ventricular tachycardia (3 beats or longer) detected during ambulatory monitoring after myocardial infarction. Circulation 1978;57:890–7.

52. Di Marco JP, Lerman BB, Kron IL, Sellers TD. Sustained ventricular tachyarrhythmias within 2 months of acute myocardial infarction: results of medical and surgical therapy in patients resuscitated from the initial episode. J Am Coll Cardiol 1985;6:759–68.

53. Marchlinski FE, Buxton AE, Waxman HL, Josephson ME. Identifying patients at risk of sudden death after myocardial infarction: value of the response to programmed stimulation, degree of ventricular ectopic

activity and severity of left ventricular dysfunction. Am J Cardiol 1983;52:1190–6.

54. Bigger JT Jr, Weld FM, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia (three or more complexes) detected with ambulatory electrocardiographic recording in the late hospital phase of acute myocardial infarction. Am J Cardiol 1981;48: 815–23.
55. Federman J, Whitford JA, Anderson ST, Pitt A. Incidence of ventricular arrhythmias in first year after myocardial infarction. Br Heart J 1978;11:1243–50.
56. Kleiger RE, Miller JP, Thanavaro S, Province MA, Martin TF, Oliver GC. Relationship between clinical features of acute myocardial infarction and ventricular runs 2 weeks to 1 year after infarction. Circulation 1981;63:64–70.
57. Maisel AS, Scott N, Gilpin E, et al. Complex ventricular arrhythmias in patients with Q wave versus non-Q wave myocardial infarction. Circulation 1985;72:963–70.
58. Mukharji J, Rude RE, Poole KW, et al. and the MILIS Study Group. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. Am J Cardiol 1984;54:31–6.
59. A Multicenter International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. Br Med J 1975;3:735–40.
60. Wilhelmsson C, Wilhelmsen L, Vedin JA, Tibblin G. Reduction of sudden deaths after myocardial infarction by treatment with alprenolol. Lancet 1974;2:1157–9.
61. Beta-blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction I. Mortality results. JAMA 1982;247:1707–14.
62. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801–7.
63. Olsson G, Rehnqvist N, Sjogren A, Erhardt L, Lundman T. Long-term treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. J Am Coll Cardiol 1985;5:1428–37.
64. Chadda K, Goldstein S, Buyington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation 1986;73:503–10.
65. Marcus FI, Cobb L, Edwards J, Kuller L, Serokman R, and the Multi-Center Post Infarction Research Group. Mortality after acute myocardial infarction in the multicenter post infarction program (abstr). J Am Coll Cardiol 1986;7:67.
66. The Multicenter Post-Infarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309: 331–6.
67. Goldstein S, Friedman L, Hutchinson R, et al. and the Aspirin Myocardial Infarction Research Group. Timing, mechanism and clinical setting of witnessed deaths in post-myocardial infarction patients. J Am Coll Cardiol 1984;3:1111–7.
68. McNamee BT, Robinson TJ, Adgey AAJ, Scott ME, Geddes JS, Pantridge JF. Long-term prognosis following ventricular fibrillation in acute ischaemic heart disease. Br Med J 1970;4:204–6.
69. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, and the Multicenter Post-Infarction Research Group. The relationships among ventricular arrhythmias left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69:250–8.
70. Luria MH, Debanne SM, Osman MI. Long-term follow-up after recovery from acute myocardial infarction. Observations on survival, ventricular arrhythmias, and sudden death. Arch Intern Med 1985;145: 1592–5.
71. Abjorn C, Karlsson E, Sonnhag C. Ventricular arrhythmias in acute myocardial infarction. Acta Med Scand 1977;201:119–25.
72. Bruschke AVG, Proudfit WL, Sones FM Jr. Clinical course of patients with normal and slightly or moderately abnormal coronary arteriograms. A follow-up study of 500 patients. Circulation 1973;42:936–45.
73. Bruschke AVG, Proudfit WL, Sones FM Jr. Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. I. Arteriographic correlations. Circulation 1973;42:1147–53.
74. Bruschke AVG, Proudfit WL, Sones FM Jr. Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5–9 years. II. Ventriculographic and other correlations. Circulation 1973;42: 1154–63.
75. Blevins RD, Kerin NZ, Frumin H, et al. Arrhythmia control and other factors related to sudden death in coronary disease patients at intermediate risk. Am Heart J 1986;111:638–44.
76. Califf RM, McKinnis RA, McNeer F, et al. Prognostic value of ventricular arrhythmias associated with treadmill exercise testing in patient studied with cardiac catheterization for suspected ischemic heart disease. J Am Coll Cardiol 1983;2:1060–7.
77. Lichtlen PR, Bethge KP, Platiel H. Incidence of sudden cardiac death in relation to left ventricular anatomy and rhythm profile. Z Kardiol 1980;69:639–48.
78. Edlin DE, Morganroth J, Iskandrian AS, Spielman SR, Horowitz LN, Kay H. Ischemia at rest is independent of the extent of ventricular dysfunction and arrhythmias in patients with coronary artery disease. Am Heart J 1985;109:228–32.
79. Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. Circulation 1985;72:681–5.
80. Huang SK, Messer JV, Denes P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. Am J Cardiol 1983;51:507–12.
81. Poll DS, Marchlinski FE, Buxton AE, Doherty JU, Waxman HL, Josephson ME. Sustained ventricular tachycardia in patients with idiopathic dilated cardiomyopathy: electrophysiologic testing and lack of response to antiarrhythmic drug therapy. Circulation 1984;70:451–6.
82. Meinertz T, Hoffman T, Kasper W, et al. Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. Am J Cardiol 1984;53: 902–7.
83. Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischemic and non-ischemic dilated cardiomyopathy; prediction of mortality by ambulatory electrocardiography. Am J Cardiol 1985;55:146–51.
84. Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy. Am J Cardiol 1984;54:147–52.
85. Baim DS, Colucci WS, Monrad ES, et al. Survival of patients with severe congestive heart failure treated with oral milrinone. J Am Coll Cardiol 1986;7:661–70.
86. Maskin CS, Siskind SJ, LeJemtel TH. High prevalence of nonsustained ventricular tachycardia in severe congestive heart failure. Am Heart J 1984;107:896–901.
87. Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: incidence, significance and effectiveness of antiarrhythmic therapy. Am Heart J 1985;109:497–504.
88. Francis GS. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence, and prognosis. Am J Cardiol 1986;57:3B–7B.
89. Graboys TB, Lown B, Podrid PJ, De Silva R. Long-term survival of patients with malignant ventricular arrhythmia treated with antiarrhythmic drugs. Am J Cardiol 1982;50:437–42.
90. Platia EV, Reid PR. Comparison of programmed electrical stimulation and ambulatory electrocardiographic (Holter) monitoring in the management of ventricular tachycardia and ventricular fibrillation. J Am Coll Cardiol 1984;4:493–500.
91. Swerdlow CD, Winkle RA, Mason JW. Determinants of survival in patients with ventricular tachyarrhythmias. N Engl J Med 1983;308: 1436–42.
92. Torres V, Tepper D, Flowers D, et al. QT prolongation and the antiarrhythmic efficacy of amiodarone. J Am Coll Cardiol 1986;7: 142–7.
93. Fogoros RN, Kelley PA, Winkle RA, Swerdlow DC, Mason JW.

Amiodarone: clinical efficacy and toxicity in 96 patients with recurrent, drug-refractory arrhythmias. Circulation 1983;68:88–94.

94. Myerburg RJ, Kessler KM, Estes D, et al. Long-term survival after prehospital cardiac arrest: analysis of outcome during an 8 year study. Circulation 1984;70:538–46.
95. Goldstein S, Landis JR, Leighton R, et al. Predictive survival models for resuscitated victims of out-of-hospital cardiac arrest with coronary heart disease. Circulation 1985;5:873–80.
96. Skale BT, Miles WM, Heger JJ, Zipes DP, Prystowsky EN. Survivors of cardiac arrest: prevention of recurrence by drug therapy as predicted by electrophysiologic testing or electrocardiographic monitoring. Am J Cardiol 1986;57:113–9.
97. Tresch DD, Keelan MH Jr, Siegel R, et al. Long-term survival after prehospital sudden cardiac death. Am Heart J 1984;108:1–5.
98. Goldberg R, Szklo M, Tonascia JA, Kennedy HL. Acute myocardial infarction. Prognosis complicated by ventricular fibrillation or cardiac arrest. JAMA 1979;24:2024–7.
99. Baum RS, Alvarez H III, Cobb LA. Survival after resuscitation from out-of-hospital ventricular fibrillation. Circulation 1974;50:1231–5.
100. Vlay SC, Reid PR, Griffith LS, Kalman CH. Relationship of specific coronary lesions and regional left ventricular dysfunction to prognosis in survivors of sudden cardiac death. Am Heart J 1984;108:1212–20.
101. Calvert A, Lown B, Gorlin R. Ventricular premature beats and anatomically defined coronary heart disease. Am J Cardiol 1977;39: 627–34.
102. Surawicz B. R on T phenomenon: dangerous and harmless. J Appl Cardiol 1986;1:39–61.
103. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. Am Heart J 1986;111:383–90.
104. Rabkin SW, Mathewson FAL, Tate RB. The electrocardiogram in apparently healthy men and the risk of sudden death. Br Heart J 1982;47:546–52.
105. Fisher FD, Tyroler HA. Relationship between ventricular premature contractions on routine electrocardiography and subsequent sudden death from coronary heart disease. Circulation 1973;47:712–9.
106. Kannel WB, Thomas HE Jr. Sudden coronary death: the Framingham Study. Ann NY Acad Sci 1982;382:3–21.
107. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130–42.
108. Dhurandhar RW, MacMillan RW, Brown KWG. Primary ventricular fibrillation complicating acute myocardial infarction. Am J Cardiol 1971;27:347–51.
109. Lie KI, Wellens HJJ, Downar E, Durrer D. Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. Circulation 1975;52:755–59.
110. Adgey AA, Devlin JE, Webb SW, Mulholland HC. Initiation of ventricular fibrillation outside hospital in patients with acute ischemic heart disease. Br Heart J 1982;47:55–61.
111. O'Doherty M, Taylor DJ, Quinn E, et al. Five-hundred patients with myocardial infarction monitored within one hour of symptoms. Br Med J 1983;286:1405–8.
112. Szlachcic J, Waters DD, Miller D, Theroux P. Ventricular arrhythmias during ergonovine-induced episodes of variant angina. Am Heart J 1984;107:20–4.
113. Plotnick GD, Fisher ML, Becker LC. Ventricular arrhythmias in patients with rest angina: correlation with ST segment changes and extent of coronary atherosclerosis. Am Heart J 1983;105:32–6.
114. Previtali M, Klersy C, Salerno JA, et al. Ventricular tachyarrhythmias in Prinzmetal's variant angina: clinical significance and relation to the degree and time course of S-T segment elevation. Am J Cardiol 1983;52:19–25.
115. Scrutinio D, De Toma L, Mangini SG, et al. Ischaemia related ventricular arrhythmias in patients with variant angina pectoris. Eur Heart J 1984;5:1013–22.
116. Kerin NZ, Rubenfire M, Willens HJ, Rao P, Cascade PN. The mechanism of dysrhythmias in variant angina pectoris: occlusive versus reperfusion. Am Heart J 1983;106:1332–40.
117. Araki H, Koiwaya Y, Nakagaki O, Nakamura M. Diurnal distribution of ST-segment elevation and related arrhythmias in patients with variant angina: a study by ambulatory ECG monitoring. Circulation 1983;67:995–1000.
118. Miller D, Waters DD, Szlachcic J, Theroux P. Clinical characteristics associated with sudden death in patients with variant angina. Circulation 1982;66:588–92.
119. Gabliani GI, Winniford MD, Fulton KL, Johnson SM, Mauritson DR, Hillis LD. Ventricular ectopic activity with spontaneous variant angina: frequency and relation to transient ST-segment deviation. Am Heart J 1985;110:40–3.
120. Bayes de Luna A, Carreras F, Cladellas M, Oca F, Sagues F, Garcia Moll M. Holter ECG study of the electrocardiographic phenomena in Prinzmetal angina attacks with emphasis on the study of ventricular arrhythmias. J Electrocardiol 1985;18:267–75.
121. Friedman LM, Byington RP, Capone RJ, Furberg CD, Goldstein S, Lichstein E. Writing group for the Beta-Blocker Heart Attack Trial Research Group. Effect of propranolol in patients with myocardial infarction and ventricular arrhythmias. J Am Coll Cardiol 1986;7: 1–8.
122. Bryson AL, Parisis A, Schechter E, Wolfson S. Life-threatening ventricular arrhythmias induced by exercise. Cessation after coronary bypass surgery. Am J Cardiol 1973;32:995–9.
123. Molajo AO, Summers GD, Bennett DH. Effect of percutaneous transluminal coronary angioplasty on arrhythmias complicating angina. Br Heart J 1985;54:375–7.
124. Maron BJ, Savage DD, Wolfson JK, Epstein SE. Prognostic significance of 24 hour ambulatory electrocardiographic monitoring in patients with hypertrophic cardiomyopathy: a prospective study. Am J Cardiol 1981;48:252–7.
125. Furberg CD, May GS. Effect of long-term prophylactic treatment on survival after myocardial infarction. Am J Med 1984;76:76–83.
126. Pratt CM, Delclos G, Wierman AM, et al. The changing baseline of complex ventricular arrhythmias. A new consideration in assessing long-term antiarrhythmic drug therapy. N Engl J Med 1985;313: 1444–9.
127. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB. Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982;65:886–94.
128. Meissner MD, Kay HR, Spielman SC, Greenspan AM, Kutalek SP, Horowitz LN. Acute antiarrhythmic drug efficacy is independently related to left ventricular function (abstr). J Am Coll Cardiol 1986;7: 130A.